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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/653,294	05/24/96	CLAYBERGER C	286002020023

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EXAMINER	
CUNNINGHAM, T	
ART UNIT	**PAPER NUMBER**
1644	25

DATE MAILED: 02/01/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/653,294	Clayberger et al.
Examiner	**Group Art Unit**
Thomas Cunningham	1644

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-26 is/are pending in the application.

Of the above, claim(s) 22-26 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-21 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 1-21 are active. The request filed on 11/13/98 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/653,294 is acceptable and a CPA has been established. An action on the CPA follows. The after final amendment (Paper No. 20) has not been entered. This action is responsive to the amendment, Paper No. 24, mailed 11/13/98.

2. A restriction was required under 35 USC 121 in the parent application, Paper No.10 between:

I. Claims 1-21 , drawn to peptide products.

II. Claims 22-25, drawn to nucleic acids.

III. Claim 26, drawn to antibodies.

Applicant elected Group I, claims 1-21 with traverse. This restriction requirement is hereby reiterated. Accordingly, claims 22-26 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. (Withdrawn) The prior rejection under 35 U.S.C. 112, second paragraph set forth in subsection I of the last action is withdrawn in view of the amendment of claim 1 to recite "consists of".

4. (Maintained) Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for particular peptides such as the sequences demonstrated to inhibit cytolysis on pages 21-et seq. of the specification, does not reasonably provide enablement for all the peptides encompassed by broad claim language.

E. (maintained) Diverse peptides. Claims 1-21 read broadly on peptides comprising residues 75-84 of any HLA-B alpha chain. However, page 21, lines 27-29 indicate that only peptides having sequences corresponding to particular alleles of HLA-B alpha 1 block CTL lytic responses. E.g. HLA-B2702 blocks, but HLAB2705 does not. It would be unpredictable which peptide species would be capable of multiallele blocking without testing of different peptide species on a case-by-case basis. For instance, pages 21-22 of the specification disclose that the HLA-B2702.75-84 and HLA-B2705.75-84 peptides, though differing in only three residues (see lines 6-7 on page 21) have materially different effects: the HLA-B2702 peptide inhibited lysis; the HLA-B2705 peptide did not.

--See arguments at end of section.

F. (Maintained) Variants. Claims 1-21 also encompass variants of the recited (HLA-B derived) peptide sequences. It would be unpredictable which mutations of an HLA-B 75-84 sequence would retain the critical functional property of being able to inhibit CTL activity because such mutations would be expected to affect functional binding of the peptide to the T cell receptor or accessory molecules. Modifications to the recited peptides, whether the addition, substitution, or deletion of amino acid residues, or the joining of such peptides to other chemical moieties would be expected to have unexpected, unpredictable effects on the activity of the particular peptide to modulate CTL responses, see e.g. Bowie, et al., Science 247:1306-1310 (1990). It is unclear how the peptides are actually modulating CTL responses, but one with skill in the art would expect that the claimed peptide compounds are interfering with the T cell receptor (TCR) antigen presenting cell interaction. It is unclear on a structural basis which types of modifications can be made to a "blocking" or stimulatory peptide and still have it exert its functional effect. For instance a stimulatory peptide that had bulky, sterically hindering chemical moieties joined to it would not be expected to effectively stimulate CTL responses, because the additional moieties would be expected to prevent it from binding to the sites on the CTL or the APC necessary for inducing CTL stimulation. Each chemical modification of a peptide known to modulate CTL activity would have to be investigated on a case-by-case basis and thus would impose a burden of undue experimentation on one with skill in the art.

--See arguments at end of section.

H. (Maintained) Immunosuppressive agent required. According to page 31 of the specification allograft survival was similar in control and peptide-treated groups. Only groups treated with CsA had significant increases in graft survival time.

--Applicant's arguments on page 18 of the response have been considered. However, claims like claim 18 have not limited to provision of the recited peptides along with an immunosuppressant. Evidence that the recited peptides alone would have activity in increasing

allograft survival would be helpful.

J. (Maintained) The compound of claim 1 appears to be a peptide homo- or heterodimer. One would expect that only certain types of dimeric compounds have the ability to reduce CTL responses because different configurations of dimers would have different structures or spacing of determinants, and therefore different functional abilities to compete or bind to T cell ligands or MHC Class I molecules. Since a particular mechanism of action for the peptide dimers has not been adequately described, it would be unpredictable which structures would retain functional activity.

--See below.

--Applicant urges that the scope of the instant claim language is supported by at least 17 separate examples of peptides and refers to Table 1 at page 21 of the specification. However, Table 1 only exemplifies dimers of the "beta-alpha variety" i.e. those comprising the (a84-79)-(aa79-84) conjugate, but it does not exemplify alpha-alpha, beta-beta or alpha-beta dimers. Different tertiary or quaternary configurations would be expected to have unpredictable effects on function. For instance, the top of page 22 of the specification indicates the unpredictability of structural variation on lytic ability, because length as well as presence of an inverted repeat dimer had different effects on cytolysis.

Further, only dimers derived from residues 75-84 of a particular HLA allelic product, HLA-B2702, are exemplified. One with skill in the art would recognize that different MHC alleles encode product with different amino acid sequences and that variation in an amino acid sequence would have unpredictable effects on functional activity. A case in point: page 22, lines 19-20 indicate that dimers formed from residues of the B7 allelic product did not inhibit CTL-mediated lysis at any concentration tested.

Applicant urges that only a limited number of peptides must be tested, and that such testing only requires routine experimentation. However, the instant claim language reads on thousands of different peptide analogs of which the Applicant has exemplified only a few as retaining an enhanced ability to modulate CTL activity. For instance for homodimers of a particular sequence consisting of only residues 79-84, there would be (2)(2)(6)(2)(2)(6)= 576 different possible analogs. However, once optional residues are figured in, as well as permutations of different heterodimers and palindromic dimers, the numbers of analogs become very great. Most of these analogs would not be expected to be functional based on the species exemplified in the specification and evidence of record. Limitation of the claims to sequences spanning residues 75-84 and occurring naturally in MHC Class I proteins, and a demonstration that a significant number of such sequences retain an ability to modulate CTL activity would be helpful in addressing this rejection.

The declaration of Dr. Clayberger, Paper No. 16, has been considered, but is directed to

less polymorphic segments of MHC Class I molecules comprising residues 75-84. It is noted that the instant claims are directed to segments spanning residues 79-84, optionally containing residues 75-78. Thus, the declaratory evidence as well as the exemplified species in the specification, do not fully support the scope of the invention as claimed.

5. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson, U.S. patent 5,073,540 or WO88/05784 (published 11 August 1988). Olsson disclose peptides useful as antagonists or agonists for membrane receptors. The prior art compounds have essentially the same structure as those of the instant application, see e.g. cols. 7 and 8. WO88/05784 discloses similar peptides, see e.g. claim 1. WO88/05784 also suggests modification of such peptides using conventional techniques to extent their biological halflives, see pages 21-23. Page 10 of the specification describes such conventional techniques.

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the prior art peptides and to test functional activity on surface receptors or lymphocyte activity of the modified peptides using the assays disclosed in Olsson col.s 12-14 or by WO88/05784 on page 25. Further, page 40 of WO88/05784 explicitly suggests use of such peptides for prolonging graft survival time by reducing rejection cytolytic CTL activity.

Claims limited to products reasonably expected to retain the unexpected properties attributed to dimeric products, such as the dimer described in Table 1, would be free of this rejection. Applicant is encouraged to contact the Examiner telephonically to discuss this issue.

--Applicant urges that there was no motivation in the prior art to produce dimers. However, one with ordinary skill in the art would at least expect that dimers of the same unit would exert the same functional effects as a monomer. It is noted that the claim language is not limited to palindromic dimers--e.g. (aa79-84)-(aa84-79). Claim 1 encompasses α-β dimers that "may be the same or different". Thus, dimers such as (aa79-84)-(aa79-84) are NOT excluded from the language of claim 1. The prior art rejection is maintained for such dimers. For palindromic dimers this rejection would be dropped.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D, J.D. whose telephone number is (703) 308-3968. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

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